EClinicalMedicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

EClinicalMedicine
Published by THE LANCET

Research Paper

Safety and Efficacy of the SNAP 12-hour Acetylcysteine Regimen for the Treatment of Paracetamol Overdose

Janice M. Pettie [a], Thomas M. Caparrotta [b], Robert W. Hunter [b], Emma E. Morrison [b], David M. Wood [c,d], Paul I. Dargan [c,d], Ruben H. Thanacoody [e], Simon H.L. Thomas [e], Muhammad E.M.O. Elamin [e], Ben Francis [f], David J. Webb [b], Euan A. Sandilands [a], Michael Eddleston [b], James W. Dear [b,*]

[a] NPIS Edinburgh, Royal Infirmary of Edinburgh, Edinburgh, UK
[b] Pharmacology, Toxicology and Therapeutics, Centre for Cardiovascular Science, University of Edinburgh, UK
[c] Clinical Toxicology, Guy's and St Thomas' NHS Foundation Trust, London, UK
[d] Faculty of Life Sciences and Medicine, King's College London, London, UK
[e] Medical Toxicology Centre, Institute of Cellular Medicine, Newcastle University, Newcastle NE2 4HH, UK
[f] Department of Biostatistics, Institute of Translational Medicine, University of Liverpool, UK

ARTICLE INFO

Article history:
Received 8 October 2018
Received in revised form 22 March 2019
Accepted 10 April 2019
Available online xxxx

Keywords:
Acute liver failure
Paracetamol
NAC
Clinical practice
Drug-induced liver injury

ABSTRACT

Background: Acetylcysteine (NAC) is effective at preventing liver injury after paracetamol overdose. The Scottish and Newcastle Anti-emetic Pre-treatment for Paracetamol Poisoning (SNAP) Study demonstrated that a 12 h NAC regimen was associated with fewer adverse drug reactions compared with the standard 21 h regimen. Here, we describe the clinical effectiveness of the SNAP NAC regimen.

Methods: The SNAP regimen, consisting of intravenous NAC 100 mg/kg over 2 h then 200 mg/kg over 10 h, was introduced to treat all paracetamol overdose patients at the Royal Infirmary of Edinburgh, the Royal Victoria Infirmary, Newcastle and St Thomas' Hospital, London. Patient data were prospectively and systematically collected before and after the change in treatment (total patients N = 3340, 21 h N = 1488, SNAP N = 1852). Health record linkage was used to determine patient outcome after hospital discharge.

Findings: There was no difference in liver injury or liver synthetic dysfunction between regimens. Hepatotoxicity (peak ALT > 1000 U/L) occurred in 64 (4.3%) and 67 (3.6%) patients, respectively, in the 21 h and SNAP groups (absolute difference −0.7%, 95% CI −2.1 to 0.6). Multivariable logistic regression did not identify treatment regimen as an outcome-associated factor. No patients were readmitted to hospital with, or died from, liver failure within 30 days of discharge. Anti-histamine treatment (for NAC anaphylactoid drug reactions) was prescribed for 163 (11.0%) patients with the 21 h regimen and 37 (2.0%) patients with the SNAP regimen (absolute difference 9.0% (95% CI 7.3 to 10.7)).

Interpretation: In clinical use the SNAP regimen has similar efficacy as standard therapy for preventing liver injury and produces fewer adverse reactions.

1. Introduction

Paracetamol (acetaminophen) overdose is one of the most common reasons for emergency hospital attendance and the leading cause of acute liver failure in the Western world [1]. Annually in the UK, paracetamol overdose results in approximately 100,000 Emergency Department presentations and 50,000 acute hospital admissions [2], and is the direct cause of death in around 150 people [3]. Deaths or episodes of acute liver failure in patients who start treatment within 8 hours (h) of a single acute overdose are extremely rare because of the ease of availability of a highly effective antidote, acetylcysteine (NAC). This antidote replenishes cellular glutathione, which protects hepatocytes against injury from the toxic paracetamol metabolite N-acetyl-p-benzoquinone imine (NAPQI)

Abbreviations: NAC, Acetylcysteine; SNAP, Scottish and Newcastle Anti-emetic Pre-treatment for Paracetamol Poisoning; RIE, Royal Infirmary of Edinburgh; RVI, The Royal Victoria Infirmary, Newcastle; STH, St Thomas' Hospital, London; NAPQI, N-acetyl-p-benzoquinone imine; MHRA, Medicines and Healthcare Products Regulatory Agency's; INR, International normalised ratio; ALT, Alanine transaminase activity.

* Corresponding author at: Centre for Cardiovascular Science, University of Edinburgh, The Queen's Medical Research Institute, 47 Little France Crescent, Edinburgh EH16 4TJ, UK.
E-mail addresses: janice.pettie@nhslothian.scot.nhs.uk (J.M. Pettie), tom.caparrotta@igmm.ed.ac.uk (T.M. Caparrotta), robert.hunter@ed.ac.uk (R.W. Hunter), emma.morrison@nhs.net (E.E. Morrison), david.wood@gstt.nhs.uk (D.M. Wood), paul.dargan@gstt.nhs.uk (P.I. Dargan), ruben.thanacoody@nuth.nhs.uk (R.H. Thanacoody), simon.thomas@newcastle.ac.uk (S.H.L. Thomas), muhammad.elamin@npis.org (M.E.M.O. Elamin), b.r.francis@liverpool.ac.uk (B. Francis), d.j.webb@ed.ac.uk (D.J. Webb), euan.sandilands@nhslothian.scot.nhs.uk (E.A. Sandilands), m.eddleston@ed.ac.uk (M. Eddleston), james.dear@ed.ac.uk (J.W. Dear).

https://doi.org/10.1016/j.eclinm.2019.04.005

Research in Context

Evidence Before This Study

Paracetamol overdose is a common reason for emergency admission to hospital and the commonest cause of acute liver failure in Europe and North America.

Acetylcysteine (NAC) is effective at preventing liver injury, but the optimal regimen has not been defined.

We have previously demonstrated that a shorter 12 h NAC regimen (the 'SNAP' regimen) produces fewer adverse reactions.

Added Value of This Study

In this study we demonstrate that the SNAP regimen has comparable effectiveness to the standard 21 h NAC regimen at preventing liver injury in 3340 patients treated at 3 UK hospitals.

Implications of All the Available Evidence

This study provides an evidence base for clinical practice to change to using the SNAP regimen as standard care for treatment of paracetamol overdose. This is because this treatment regimen improves treatment safety for this patient group, reduces the need for treatment interruptions and potentially shortens the length of treatment without compromising the effectiveness of NAC at preventing liver injury.

[4]. Since 2012, revised guidelines for the NAC treatment of paracetamol poisoning have been implemented in the UK. These guidelines recommend treating all patients with a paracetamol concentration above a single treatment line on the paracetamol nomogram (the 100 mg/L at 4 h after overdose treatment line — '100-line') and treating all patients with a staggered overdose or uncertain time of ingestion [5].

NAC has been administered intravenously using the same 21 h regimen since the 1970s with few dose-finding studies being performed in this area. This regimen consists of three sequential, weight-related, doses of NAC given intravenously in 5% dextrose: 150 mg/kg body weight over 15 min (extended in the UK to 1 h in 2012), followed by 50 mg/kg over 4 h and 100 mg/kg over 16 h. This NAC regimen is associated with a high incidence of adverse drug reactions (ADRs), in particular anaphylactoid reactions [6]. These are unpleasant for patients, result in temporary cessation of therapy, require anti-histamine treatment, extend the duration of treatment and hospitalisation, and sometimes cause doctors to withhold NAC. In addition to ADRs, other problems are that medication errors occur because the NAC regimen is complex [7] and treatment leads to significant hospital bed occupancy because the regimen is time consuming (around 47,000 bed days per year in England) [2].

To address these issues with the 21 h NAC regimen different treatment regimens have been introduced into clinical practice. These include simplified 1 or 2 'bag' regimens [8,9] or stopping NAC before the end of the 21 h regimen in very low risk patients [10]. To date, these regimens have not been assessed with robust studies to determine efficacy and safety, We used pharmacokinetic modelling to design a 12 h NAC regimen (known as the Scottish and Newcastle Anti-emetic Pretreatment for Paracetamol Poisoning Study regimen or "SNAP regimen") which delivers the same dose of NAC as the 21 h regimen (300 mg/kg) but does not result in the high early blood NAC concentrations associated with anaphylactoid reactions and other ADRs [11]. A randomised clinical trial that compared the SNAP NAC regimen to the standard 21 h NAC regimen reported a substantial reduction in ADRs with the new regimen [6].

Due to the reduction in ADRs, simplicity and apparently equivalent effectiveness, clinical units have started to use the SNAP regimen. On 28th September 2015 it was adopted into clinical practice for all patients requiring NAC treatment for paracetamol overdose at the Royal Infirmary of Edinburgh (RIE), UK. Clinical outcome was recorded in the long-running prospective audit of paracetamol poisoning within the RIE from before and after the change. On 1st June 2016 and 1st October 2016, the SNAP regimen was introduced into routine clinical practice for all patients at St Thomas' Hospital (STH), London and the Royal Victoria Infirmary (RVI), Newcastle, respectively. Here we compare the effectiveness of the SNAP regimen with that of the 21 h regimen in an observational study involving 3340 unselected patients with paracetamol poisoning.

2. Methods

2.1. Edinburgh Patient Data

Patient data were collected as part of a long-running, prospective, audit of consecutive patients admitted with paracetamol overdose to RIE. This hospital provides the only Emergency Department for the City of Edinburgh, UK. The change to using the SNAP regimen was a clinical decision approved by the local NHS governance process. The NHS Caldicott Guardian approved collection of data using the Toxicology Unit's paracetamol care pathway data collection form. Prospective data collection, using a proforma, encompassed two years before and after the introduction of the SNAP regimen (4 years total).

We included all consecutive patients admitted to RIE with paracetamol overdose that required NAC according to current UK management guidelines. The UK criteria for starting treatment with NAC are described in detail on the UK poisons management database TOXBASE (www.toxbase.org). In brief, patients taking a single acute overdose (all tablets ingested within 1 h) were treated if their timed blood paracetamol concentration was above the 100-line. The decision to treat patients taking a staggered overdose (deliberate overdose over more than 1 h) was based on the Medicines and Healthcare Products Regulatory Agency's (MHRA) guidance published in 2012, which stated that all patients should receive NAC [5]. There were no changes to the guidelines during the 4-year period of this study. The pattern of overdose referred to as therapeutic excess is defined as an accidental overdose with the tablets taken for therapeutic indications.

From 28 September 2013 to 27 September 2015 patients received intravenous NAC using the 21 h NAC regimen: 150 mg/kg body weight over 1 h, followed by 50 mg/kg over 4 h and 100 mg/kg over 16 h (300 mg/kg total). One hour before the end of treatment blood was drawn for measurement of liver function tests, creatinine and international normalised ratio (INR) to determine whether treatment could be safely stopped after 21 h of NAC using the criteria outlined below.

From 28 September 2015 to 27 September 2017 patients were treated with the SNAP regimen: 100 mg/kg over 2 h then 200 mg/kg over 10 h (300 mg/kg total). Two hours before the end of this 12 h treatment regimen blood was drawn and NAC treatment was stopped after 12 h if the following criteria were satisfied: INR 1.3 or less; and alanine transaminase activity (ALT) <100 U/L and not more than doubled from admission; and paracetamol concentration <20 mg/L. If these criteria were not reached then NAC was continued at 200 mg/kg over a further 10 h. Irrespective of whether NAC was continued or discontinued, the local protocol was for patients to have further blood sampling 20 h after starting NAC to determine the need for extended treatment (at the equivalent time to the 21 h regimen). For the 21 h and SNAP regimens the same UK national criteria for stopping NAC treatment after 21 h were used: INR 1.3 or less and ALT < 100 U/L and ALT not more than doubled from admission. Blood results were collected from TrakCare software application (InterSystems Corporation, Cambridge, Massachusetts), an electronic patient record system used by the Acute

Please cite this article as: J.M. Pettie, T.M. Caparrotta, R.W. Hunter, et al., Safety and Efficacy of the SNAP 12-hour Acetylcysteine Regimen for the Treatment of Paracetamol Over..., , https://doi.org/10.1016/j.eclinm.2019.04.005

Hospitals Division of Lothian National Health Service (NHS) Health Board, Scotland.

2.2. London and Newcastle Patient Data

Data were collected during previous audits of use of the conventional 21 h NAC regimen following implementation in September 2012. The SNAP regimen was introduced on 1st June 2016 and 1st October 2016 at STH and RVI, respectively, after approval by the local NHS clinical governance process. Data were collected with local approval from the Caldicott Guardian. All paracetamol overdose patients requiring NAC were identified for treatment using the same national criteria as RIE. The 21 h regimen was delivered as per RIE. For SNAP treatment, the same patient care pathway was used at STH and RVI; and the same 12 h SNAP regimen was used at all 3 sites. At the end of the 12 h SNAP regimen blood samples were taken for liver function, creatinine, INR and paracetamol concentration; if these blood tests were less than 24 h after the last dose of paracetamol, the blood tests were repeated at 24 h. NAC was continued if the following criteria were met on either of these blood tests: ALT more than 2 × upper limit of normal or doubled from admission, or INR more than 1.3, or paracetamol concentration more than 10 mg/L. Blood results were collected from the STH and RVI local electronic patient record systems.

2.3. Identification of Anaphylactoid Reactions and Liver Toxicity

In all 3 centres anti-histamine prescribing was used to estimate the rate of anaphylactoid reactions with both the 21 h and SNAP regimens. The diagnosis of paracetamol-induced liver injury was made from ALT and INR measurement. The peak value from each hospital admission was used for analysis.

2.4. Scottish Data Linkage

Hospital admission and mortality data were obtained from the national hospitalisation register (Scottish Morbidity Record, SMR01) and the National Records of Scotland death registrations, respectively. The SMR01 is a population-based register of hospital admission episodes occurring in Scotland, and holds information on patient conditions leading to admission. Ethical approval to use fully anonymised collated data was provided by National Services Scotland Information Governance. Index cases admitted to RIE were identified where the ICD-10 diagnosis code T39.1 (Poisoning by, adverse effect of and underdosing of 4-Aminophenol derivatives) was present as either the primary diagnosis or was present in any diagnostic position. The time windows for analysis were 28th September 2012 to 27th September 2015 (21 h NAC regimen) and 28th September 2015 to 27th September 2017 (SNAP regimen). The following outcomes were measured and expressed as rate per 1000 admissions: incidence of hospital readmission within 7 days and 30 days of the index case (due to liver failure (see below for definition), paracetamol overdose (T39.1), all other causes), death within 7 days and within 30 days of index case (liver failure, all other causes) and transfer to the Scottish Liver Transplant Unit (7 days and 30 days of index case). Liver failure was defined by ICD-10 codes K72 hepatic failure NEC, K711 Toxic liver failure with hepatic necrosis (includes hepatic failure (acute) (chronic) due to drugs). The Scottish Liver Transplant Unit is the only transplant unit covering the Scottish population.

2.5. Statistical Analysis

Liver injury was quantified by multiple cut-off values for ALT and INR. Hepatotoxicity was defined as a peak ALT > 1000 U/L and this definition was used as the outcome for subsequent statistical analysis. Due to slight differences in the delivery of the SNAP regimen across centres we have considered the data from RVI and STH together and they are presented both separately and combined with data from RIE. The data are presented as the number of cases expressed as a percentage of the relevant total. For liver injury the denominator used was the respective number of patients starting NAC treatment (unless otherwise stated). Proportions were compared across treatment groups by the method described by Newcombe (1998 — method 10) [12]. Differences are presented as the absolute percentage change and 95% confidence intervals. Positive absolute changes indicate a higher proportion in the SNAP regimen group than in the 21 h NAC regimen treated group. For data from Scottish data linkage the numbers are represented as rate per 1000 admissions.

We used R, version 3.4.4, for multivariable logistic regression analyses to assess the strength of association between a combination of patient variables and both hepatotoxicity (ALT > 1000 U/L) and hepatic synthetic dysfunction (INR > 2). The following variables were included in this analysis: patient age, gender, weight, paracetamol dose ingested, dose ingestion per kg body weight, presentation ALT before NAC started, presentation paracetamol concentration, presentation INR, presentation serum creatinine concentration, position on paracetamol treatment nomogram (single acute overdose only), time from overdose to starting NAC (single acute overdose only), treatment centre and treatment protocol (21 h or SNAP). Position on the nomogram was derived from the paracetamol concentration and time from overdose to blood sampling using nomograms based on the standard Rumack-Matthew and Prescott nomograms [13,14]: ND (paracetamol not detected), <100, 100–149, 150–199, 200–299 and >300 mg/L. All continuous variables were scaled and mean centred to aid meaningful interpretation of the intercept. Due to the predictive interest of the study, patients with the following data were excluded: missing value for presentation ALT (85 patients), missing value for presentation INR (417 patients), presentation ALT > 1000 U/L (40 patients) and/or presentation INR > 2 (39 patients). The dataset was split into acute single overdose with complete data (1549 patients) and staggered overdose and therapeutic excess with complete data (1001 patients). Separate models were derived for these two sub-datasets. Singular variables that were significant ($p < 0.05$) in univariable logistic regression were entered into stepwise selection processes to obtain a final multivariable model.

Based on clinical expertise, it was hypothesised that the SNAP protocol could have a differing effect in those presenting later at hospital (more than 8 h) after an acute single overdose compared to those presenting before. To test this hypothesis, an interaction term of the binary indicator of time from overdose to starting NAC being greater than 8 h and the treatment protocol was fitted with the factors in the final model.

2.6. Role of Funding Source

The Association of Physicians UK Young Investigator Award was used to fund health record data linkage. This funder had no involvement in data analysis or paper writing.

3. Results

3.1. Edinburgh Data

In the two-year period preceding the change of regimen there were 1350 patients admitted to RIE with a diagnosis of paracetamol overdose. Of these, 1075 (79.6%) were treated with the conventional intravenous 21 h NAC regimen. After clinical adoption of the SNAP regimen 1272 patients were admitted and 1137 (89.4%) were treated. There were no demographic differences between the patient populations, although there were proportionally more patients starting NAC 8–24 h after a single acute overdose in the pre-change cohort and proportionally more staggered overdoses in the SNAP cohort (Table 1). The patient flow before and after regimen change is presented in Supplementary Fig. 1. Follow-on blood results at 20 h after starting NAC were available in

Please cite this article as: J.M. Pettie, T.M. Caparrotta, R.W. Hunter, et al., Safety and Efficacy of the SNAP 12-hour Acetylcysteine Regimen for the Treatment of Paracetamol Over..., , https://doi.org/10.1016/j.eclinm.2019.04.005

843 (74.1%) SNAP treated patients (Supplementary Fig. 1; the reasons for 20 h blood results not being available are described in Supplementary Table 1). The 10 h blood results for patients without follow-on 20 h results demonstrated the following values: median (IQR): paracetamol concentration 5 mg/L (<5–7); ALT 17 U/L (12–27); INR 1.2 (1.1–1.2). Of these there were 29 patients with an ALT activity greater than the local upper limit of normal (50 U/L) at 10 h (median 82 U/L (65–131, maximum 961)). In 23 of the 29 patients their ALT activity had fallen from admission to 10 h (mean decrease 25 U/L). The overdose types of these SNAP treated patients — who had 10 h bloods without 20 h bloods — were 79% single acute ingestions who presented within 8 h of overdose, 9% acute presenting greater than 8 h and 12% staggered overdose. All acute ingestions were below the 200 line on the nomogram, 69% were below the 150 line.

In the 2-year period using the conventional 21 h NAC regimen 127 (11.8%) of the treated RIE patients had an anaphylactoid reaction as estimated by prescription of an anti-histamine drug. By contrast, in the 2-year period using the SNAP regimen 18 (1.6%) of the treated patients received anti-histamine treatment. This represents an absolute risk reduction (ARR) of 10.2% (95% CI 8.2 to 12.4; number needed to treat to prevent one anti-histamine prescription 10). Within the time windows included in this study, 37 patients were treated with NAC at RIE both before and after the regimen change, representing 198 admission episodes of which 81 episodes were treated with the 21 h NAC regimen and 117 with the SNAP regimen. In these repeat-presenting patients, anaphylactoid reactions occurred 5 times with the 21 h regimen (6.2% of total episodes) and once with the SNAP regimen (0.9%) (ARR: 5.3% (95% CI 0.1 to 12.8)).

Table 2 presents the comparison of the effectiveness of the two regimens with regard to preventing liver injury as quantified by the peak hospital stay ALT activities and INR values. These data are presented as a proportion of those patients commencing NAC treatment. Hepatotoxicity (peak ALT > 1000 U/L) occurred in 47 patients (4.4%) with 21 h NAC and 44 patients (3.9%) with SNAP (absolute difference −0.5%, 95% CI −2.2 to 1.2). When hepatotoxicity is represented as a proportion of those patients who had blood sampling at 20 h after starting NAC the absolute difference between regimens was 0.6% (95% CI −1.4 to 2.6. 21 h regimen 47/1009, SNAP 44/843).

3.2. London and Newcastle Data

At RVI and STH 413 patients were treated with the 21 h NAC regimen and 715 patients were treated with the SNAP regimen. The demographics of these patients are presented in Table 1. Anti-histamine treatment was prescribed for 36 (8.7%) patients treated with the 21 h regimen and 19 (2.7%) patients treated with the SNAP regimen (ARR 6.1% (95% CI 3.3 to 9.3)). With the 21 h and SNAP regimens, hepatotoxicity (peak ALT > 1000 U/L) occurred in 17 (4.1%) and 23 (3.1%) patients, respectively (absolute difference −0.9%, 95% CI −3.5 to 1.3) (Table 2).

3.3. Combined Data

When all patients were included (21 h N = 1488, SNAP N = 1852) anti-histamine treatment was prescribed for 163 (11.0%) patients with the 21 h regimen and 37 (2.0%) patients with the SNAP regimen (ARR 9% (95% CI 7.3 to 10.7)). Fig. 1 presents the absolute differences in the percentage of patients developing liver injury. Hepatotoxicity occurred in 64 (4.3%) and 67 (3.6%) patients in the 21 h and SNAP treatment groups, respectively (absolute difference −0.7%, 95% CI −2.1 to 0.6) (Table 2).

Multivariable logistic regression analysis was performed to explore the relationship between treatment regimen and known factors associated with liver injury (Supplementary Table 2). Five factors were significant (p = 0.05 or less) predictors of a peak ALT > 1000 U/L as the outcome in acute single overdose patients: The magnitude of these effects were ordered as "ND" nomogram ($\beta = -6.9$, reduction in outcome probability) (p = 0.0012), INR ($\beta = 0.99$, increase) ($p = 3.7 \times 10^{-13}$), paracetamol concentration ($\beta = 0.73$, increase) ($p = 2.8 \times 10^{-7}$), ALT ($\beta = 0.64$, increase) ($p = 8.4 \times 10^{-9}$) and the time from overdose to starting NAC treatment ($\beta = 0.42$, increase) ($p = 4 \times 10^{-4}$). The beta-coefficients represent the increase in the value of the outcome variable for each one standard deviation increase in the covariate's value. With ALT > 1000 U/L as the outcome in staggered and therapeutic excess patients, there were 3 statistically significant factors at presentation. The magnitude of these effects was ordered as INR ($\beta = 0.77$, increase) ($p = 2 \times 10^{-5}$), paracetamol concentration ($\beta = 0.66$, increase) (p = 0.0019) and ALT ($\beta = 0.49$, increase) ($p = 2.8 \times 10^{-4}$).

With INR > 2 as the outcome in acute single overdose patients, there were 3 statistically significant factors at presentation: INR ($\beta = 1.1$, increase) ($p = 6.9 \times 10^{-13}$), paracetamol concentration ($\beta = 0.91$, increase) ($p = 9.2 \times 10^{-9}$) and ALT ($\beta = 0.33$, increase) ($p = 9.6 \times 10^{-5}$). In staggered and therapeutic excess patients, the same 3 factors were statistically significant: INR ($\beta = 0.93$, increase) ($p = 3.5 \times 10^{-7}$), paracetamol concentration ($\beta = 0.72$, increase) ($p = 8.4 \times 10^{-4}$) and ALT ($\beta = 0.25$, increase) (p = 0.032).

The treatment regimen used was not a significant factor in any of the 4 models, with the lowest p-value (p = 0.07) being observed in covariate testing with the ALT > 1000 U/L outcome in staggered patients (SNAP protocol reducing the frequency of the outcome). Further p-values (0.30, 0.43 and 0.26) for the ALT > 1000 U/L outcome in acute single overdose, INR > 2 outcome in acute single overdose and INR > 2

Table 1
Patient demographics. Patients are grouped by hospital and NAC treatment regimen. RIE = Royal Infirmary of Edinburgh. RVI = Royal Victoria Infirmary, Newcastle. STH = St Thomas' Hospital London. 21 h regimen is the conventional NAC treatment, 12 h regimen is the SNAP regimen. Data are presented as median and IQR or numbers and percentage. P values for comparison between the RIE treatment regimens were obtained by Mann–Whitney U test or test of proportions. ALT is the serum alaninine transaminase activity. ULN = upper limit of normal.

	RIE 21 h regimen N = 1075	RIE 12 h regimen N = 1137	RIE 21 h v 12 h P value	STH & RVI 21 h regimen N = 413	STH & RVI 12 h regimen N = 715	STH & RVI 21 h v 12 h P value
Demographics						
Age (years) (IQR)	32 (21–44)	33 (22–45)	0.06	30 (22–45)	32 (23–48)	0.2
Female (number, (%))	755 (70)	806 (71)	0.6	237 (57)	425 (59)	0.5
Dose ingested:						
Single overdose (median mg/kg (IQR))	212 (148–294)	217 (151–314)	0.3	250 (175–370)	229 (159–333)	1.0
Repeated overdose (median mg/kg (IQR))	145 (109–222)	151 (113–213)	0.8	180 (117–308)	170 (119–263)	0.3
Time to starting NAC after overdose:						
<8 h (number, (%))	530 (49)	520 (46)	0.2	131 (32)	230 (32)	1.0
8–24 h (number, (%))	160 (15)	126 (11)	0.005	95 (23)	124 (17)	0.01
>24 h (number, (%))	36 (3)	28 (2)	0.1	12 (3)	17 (2)	0.3
Staggered overdose (number, (%))	177 (16)	292 (26)	<0.0001	89 (22)	154 (22)	1.0
Therapeutic excess (number, (%))	164 (15)	164 (14)	0.8	62 (15)	157 (3)	<0.0001
ALT > ULN at presentation (number, (%))	162 (15)	190 (17)	0.2	64 (15)	91 (13)	0.3
Received activated charcoal (number, (%))	3 (0.3)	9 (0.8)	0.1	6 (1.5)	23 (3.2)	0.07

Please cite this article as: J.M. Pettie, T.M. Caparrotta, R.W. Hunter, et al., Safety and Efficacy of the SNAP 12-hour Acetylcysteine Regimen for the Treatment of Paracetamol Over..., , https://doi.org/10.1016/j.eclinm.2019.04.005

Table 2
Frequency of liver injury after paracetamol overdose. Patients are grouped by hospital and NAC treatment regimen. RIE = Royal Infirmary of Edinburgh. RVI = Royal Victoria Infirmary, Newcastle. STH = St Thomas' Hospital London. 21 h regimen is the conventional NAC treatment, 12 h regimen is the SNAP regimen. Data from the 2 regimens are compared by presenting the absolute difference in percentage of patients with the defined degree of liver injury and 95% confidence intervals of that difference. All patients are included from the 3 hospital sites.

	RIE 21 h regimen	RIE 12 h regimen	RIE Absolute % difference (95% CI)	STH & RVI 21 h regimen	STH & RVI 12 h regimen	STH & RVI Absolute % difference (95% CI)	21 h v 12 h overall absolute % difference (95% CI)
Number of patients starting NAC	1075	1137	–	413	715	–	–
Extended treatment beyond 21 h (N, (%))	113 (11)	131 (12)	1.0 (−1.6 to 3.6)	47 (11)	40 (6)	−5.8 (−9.5 to 2.5)	−1.5 (−3.6 to 0.5)
Peak ALT > 100 U/L (N, (%))	131 (12)	141 (12)	0.2 (−2.5 to 3.0)	48 (12)	77 (11)	−0.9 (−4.8 to 2.8)	−0.3 (−2.5 to 1.9)
Peak ALT > 150 U/L (N, (%))	108 (10)	109 (10)	0.5 (−3.0 to 2.0)	18 (4)	56 (8)	3.5 (0.5 to 6.2)	0.4 (−1.5 to 2.3)
Peak ALT > 1000 U/L (N, (%))	47 (4)	44 (4)	−0.5 (−2.2 to 1.2)	17 (4)	23 (3)	−0.9 (−3.5 to 1.3)	−0.7 (−2.1 to 0.6)
Peak INR > 2 (N, (%))	35 (3)	37 (3)	0 (−1.5 to 1.5)	10 (2)	23 (3)	0.8 (−1.4 to 2.7)	0.2 (−1.0 to 1.4)
Peak INR > 3 (N, (%))	16 (2)	17 (2)	0 (−1.1 to 1.1)	3 (1)	9 (1)	0.5 (−1.0 to 1.7)	0.1 (−0.7 to 0.9)

outcome in staggered and therapeutic excess patients suggests no significant difference in endpoints in SNAP protocol patients compared to the standard 21 h antidote regimen patients.

3.4. Pattern of Overdose

Patients taking staggered overdoses and those who start treatment with NAC later than 8 h after a single overdose are at greater risk of liver injury. Therefore, we analysed the combined dataset by overdose type (Fig. 2). With regard to the endpoint of ALT > 1000 U/L there was an effect that favoured the 21 h regimen in the 8–24 group (absolute difference 3.7% (0.5 to 7.2)) and an effect that favoured SNAP in the staggered group (absolute difference −2.9% (−6.0 to −0.6)) (Supplementary Table 3). Taking into account the optimal multivariable model for baseline variables (described above) in the late presenting patients resulted in a non-significant p-value of 0.06 for ALT > 1000 U/L. As already described, in the multivariable model derived for staggered overdoses, treatment regimen is not a significant factor when baseline variables are accounted for (p = 0.07). There was no effect of regimen on reaching the endpoint INR > 2 in any sub-group (Supplementary Table 3). Patients taking larger paracetamol overdoses are at higher risk of liver injury [15,16]. Therefore, we analysed the combined dataset by nomogram position (Supplementary Table 4). There was no difference between the two NAC regimens. If we reflect clinical practice worldwide and focus on those patients over the 150 line there was no difference between regimens (ALT > 1000: 21 h 20/485; SNAP 20/474. Absolute difference 0.1% (−2.5 to 2.7)). For those patients treated with the SNAP regimen, the number of bags of NAC received by different nomogram groups is presented in Supplementary Fig. 2. The mode average number of bags was 2 for all groups but the number of patients receiving extended treatment is increased in the higher nomogram bands.

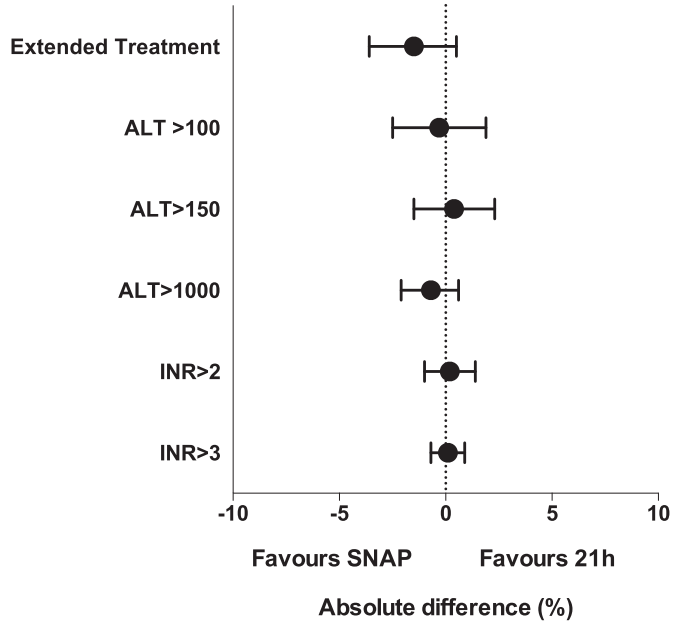

Fig. 1. The difference in the frequency of liver injury between the 21 h NAC regimen and the SNAP regimen. A range of cut-off values for serum ALT activity and INR are presented. Extended treatment refers to having NAC treatment continued after the regimen finishes. Data are presented as the absolute differences (%) with the error bars representing the 95% confidence intervals. All patients are included from the 3 hospital sites.

3.5. Scottish Health Record Linkage

Data linkage using national Scottish datasets was performed to determine patient outcome after discharge. This approach captures admissions to all Scottish hospitals and all deaths and facilitates efficient patient follow up to determine pre-defined outcomes. In those RIE patients coded with paracetamol overdose (T39.1) as their primary discharge diagnosis or with T39.1 recorded in any diagnostic position, none were readmitted with, or died from, liver failure within 7 or 30 days of their index presentation. The incidence of transfer to the Scottish Liver Transplantation Unit was similar in the time windows corresponding to RIE using the 21 h and SNAP regimens (Table 3).

4. Discussion

Paracetamol overdose is one of the most common medical emergencies in the UK and worldwide. NAC is an effective antidote but the widely used 21 h regimen produces a high rate of ADRs and necessitates prolonged hospital admission. We have previously shown that the shorter 'SNAP' regimen is associated with improved patient safety due to a substantial reduction in the incidence of anaphylactoid reactions. We now show in this paper that the two regimens are of similar efficacy in unselected patients.

The SNAP trial recruited a selected sub-group of single acute paracetamol overdose patients that were able and willing to consent to this randomised controlled trial. In the present paper we describe extension of the SNAP regimen into routine clinical practice. The SNAP trial was not large enough to confidently inform clinicians about whether the SNAP 12 h regimen is as effective as the 21 h regimen at preventing liver toxicity. In the present study, we have combined data from three specialist UK clinical toxicology units in Edinburgh, Newcastle and London to describe the safety and efficacy of the SNAP regimen when used in routine clinical practice. In the population as a whole the SNAP regimen is as effective as the 21 h NAC regimen with regard to preventing liver injury. The width of the confidence intervals in our point estimates of the difference between the 21 h and SNAP regimens could be used as a guide as to whether national guidelines and individual hospitals should switch to using the 12 h regimen or whether larger studies are still required. For example, if 4% of patients develop an ALT > 1000 U/L with the 21 h NAC regimen, clinicians can have 95% confidence that the 12 h regimen will lead to no

Please cite this article as: J.M. Pettie, T.M. Caparrotta, R.W. Hunter, et al., Safety and Efficacy of the SNAP 12-hour Acetylcysteine Regimen for the Treatment of Paracetamol Over..., , https://doi.org/10.1016/j.eclinm.2019.04.005

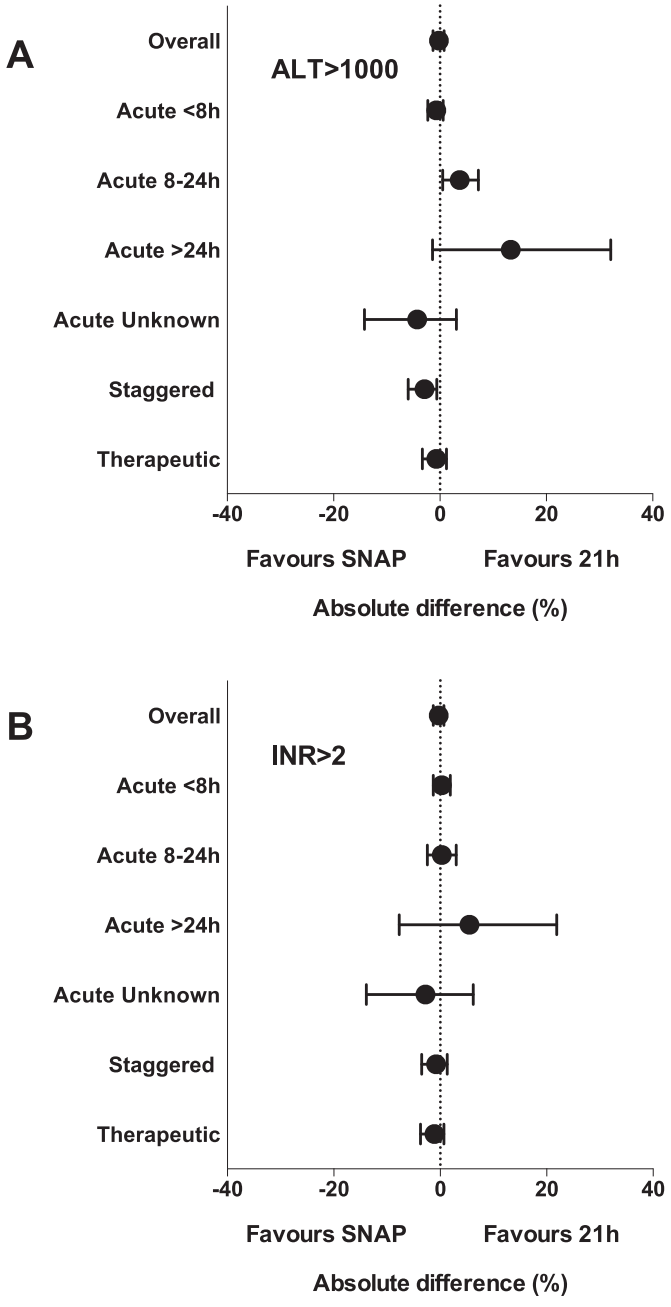

Fig. 2. The difference in the frequency of liver injury between the 21 h NAC regimen and the SNAP regimen when the population is sub-divided by overdose pattern. Liver injury is presented as ALT > 1000 U/L (A) and INR > 2 (B). Acute single overdoses are sub-divided by the time from overdose to starting NAC treatment. The unknown group took a single overdose at an unknown time. Staggered and therapeutic excess patterns are also presented. Data are presented as the absolute differences (%) with the error bars representing the 95% confidence intervals. Patients without baseline ALT or INR values and those reaching the endpoints before starting NAC were excluded. Patients from all 3 sites are included.

more than 4.6% of patients developing this magnitude of increase in ALT activity.

This paper demonstrates reduced anaphylactoid reactions in unselected patient populations treated with the SNAP regimen across 3 UK hospitals. While such reactions are not usually life-threatening, they are unpleasant and lead to treatment interruption, treatment refusal and reluctance of physicians to treat patients with a history of previous reactions. In the Edinburgh dataset there were a number of patients who were treated with both the 21 h NAC and SNAP regimens. In these repeat presenters the incidence of anaphylactoid reactions was

Table 3
Patient outcomes derived from data linkage of Royal Infirmary of Edinburgh admissions with paracetamol overdose (T39.1 code ICD10) as the primary diagnosis or anywhere in the diagnostic coding. Patient admissions were from 28th September 2012–28th September 2015 (21 h regimen) and 28th September 2015–27th September 2017 (12 h regimen). For the primary diagnosis table N numbers were 1913 and 1031 for the 21 h and 12 h regimens. For the any diagnostic position table N numbers were 3017 and 1507 for the 21 h and 12 h regimens. Data are presented as the number and the percentage of admissions.

	RIE 21 h regimen	RIE 12 h regimen	Absolute difference (95% CI)
Primary diagnosis T39.1			
Readmission in 7 days			
Liver failure	0	0	0% (−0.3 to 0.2)
Paracetamol OD	29 (1.5)	17 (1.7)	0.1% (−0.7 to 1.2)
All other cases	45 (2.4)	23 (2.2)	−0.1% (−1.2 to 1.1)
Readmission in 30 days			
Liver failure	0	0	0% (−0.3 to 0.2)
Paracetamol OD	81 (4.2)	66 (6.4)	2.1% (0.5 to 4)
All other cases	136 (7.1)	72 (7.0)	−0.1% (−1.9 to 1.9)
Death within 7 days			
Liver failure	0	0	0% (−0.3 to 0.2)
All other cases	0	1 (0.2)	0.1% (0.1 to 0.5)
Death within 30 days			
Liver failure	0	0	0% (−0.3 to 0.2)
All other cases	0	1 (0.2)	0.1% (0.1 to 0.5)
Liver unit transfer			
7 days	4 (0.4)	1 (0.2)	−0.1% (−0.5 to 0.4)
30 days	6 (0.6)	1 (0.2)	−0.2 (−0.6 to 0.3)
Any position T39.1			
Readmission in 7 days			
Liver failure	0	0	0% (−0.1 to 0.3)
Paracetamol OD	32 (1.1)	21 (1.4)	0.3% (−0.3 to 1.1)
All other cases	63 (2.1)	36 (2.4)	0.3% (−0.5 to 1.3)
Readmission in 30 days			
Liver failure	0	0	0% (−0.1 to 0.3)
Paracetamol OD	90 (3.0)	76 (5.0)	2.1% (0.9 to 3.4)
All other cases	190 (6.3)	114 (7.6)	1.3% (−0.2 to 2.9)
Death within 7 days			
Liver failure	0	0	0% (−0.1 to 0.3)
All other cases	2 (0.1)	1 (0.1)	0% (−0.1 to 0.3)
Death within 30 days			
Liver failure	0	0	0% (−0.1 to 0.3)
All other cases	14 (0.9)	1 (0.1)	−0.4% (−0.04 to −0.7)
Liver unit transfer			
7 days	10 (0.6)	2 (0.2)	−0.2% (−0.5 to 0.2)
30 days	12 (0.7)	2 (0.2)	−0.3 (−0.6 to 0.1)

reduced, suggesting that patients who have had reactions to the 21 h NAC regimen are less likely to have a repeat reaction if treated with the SNAP regimen. This current paper reproduces the principal findings from the SNAP trial in routine clinical practice, and thus provides external validity.

The SNAP regimen is shorter than current treatment so has the potential to reduce length of hospital stay for patients who do not develop liver toxicity. Defining the criteria for discharge from hospital immediately after completing the 12 h SNAP regimen will be a focus for future research and guideline development. In both the 21 h regimen and SNAP the dose of NAC is based solely on body weight and not any of the variables identified as being associated with increased risk of liver injury in our models (presentation paracetamol concentration, ALT and INR). Further clinical data and research will be needed to determine whether there are sub-groups of patients who would be optimally treated with lower or higher doses of NAC, such as patients presenting following large overdoses [15,16], and/or whether other biomarkers currently being developed could help identify patients at greater risk [17].

4.1. Limitations

From the data in this paper we cannot confidently determine whether there are sub-groups of overdose patients that would be better treated with the 21 h or SNAP protocol. When clinically relevant sub-

Please cite this article as: J.M. Pettie, T.M. Caparrotta, R.W. Hunter, et al., Safety and Efficacy of the SNAP 12-hour Acetylcysteine Regimen for the Treatment of Paracetamol Over..., , https://doi.org/10.1016/j.eclinm.2019.04.005

groups were investigated, the SNAP protocol appeared better in staggered overdose and the 21 h protocol better in late presenting single overdoses. However, these effects were not significant once differences in baseline variables were adjusted for. In patients with high blood paracetamol concentrations the two regimens did not differ. Substantially larger studies are required to identify any real sub-group differences. This paper describes the results of an observational study before and after a change in treatment so is inherently at risk of confounding associated with this study type. However, it is reassuring that the patient groups were largely similar in their demographics and there were no changes to the management of paracetamol overdose other than the introduction of the SNAP regimen in the study period. Furthermore, the assessment of efficacy by use of blood results and data linked outcomes is relatively objective. This report uses blood results from routine clinical practice and there are therefore missing data. For example, there were significantly more patients in the SNAP regimen who did not have blood taken at 20 h. This is because the addition of blood sampling at the end of the 12 h regimen gave patients and treating clinicians the confidence to omit the repeat blood tests at 20 h. Those patients without blood results at 20 h had 10 h blood results that indicate most were at low risk of developing subsequent liver injury, but this cannot be excluded. Data linkage demonstrated that no patients returned to any hospital in Scotland with liver failure at 7 and 30 days after discharge. Furthermore, the overall hospital readmission rate was similar for the 21 h NAC and SNAP regimens. This suggests that the patients who did not have blood tests at 20 h did not come to serious harm after hospital discharge. Finally, NAC can cause small increases in INR in the absence of liver injury and this phenomenon could account for a small proportion of the cases of INR > 2 rise [18]. As the SNAP regimen delivers NAC at a faster rate, in the absence of liver injury it can produce a larger increase in INR compared to the 21 h regimen (a false positive result). However, this NAC-induced increase in INR is unlikely to exceed the INR > 3 cut-off used in this paper.

In summary, 2 years of experience of using the SNAP regimen confirms that it produces fewer ADRs and has similar efficacy with regard to preventing liver injury when compared to the 21 h NAC regimen. Further clinical development and adoption of the SNAP regimen could improve treatment safety for this patient group, reduce the need for treatment interruptions and potentially shorten the length of treatment without compromising antidote effectiveness.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eclinm.2019.04.005.

Funding

Supported by the Association of Physicians, UK.

Declarations of Interest

The authors have nothing to declare.

Authors' contributions

JMP collected the RIE data; TMC, RWH, EEM and BF performed the analysis. BF was the named statistician. DMW and PID led recruitment from STH. RHT, SHLT and MEMOE led recruitment at RVI; DJW, EAS, ME, SHLT and JWD designed the analysis. JWD was the lead investigator.

Search strategy and selection criteria

Pubmed was used as the primary database to identify relevant publications.

Acknowledgements

We thank the contribution of the following people to this study: Margaret A Dow, Eibhlin Brogan, Elizabeth Macrae, Aravindan Veiraiah, Jonathan Wraight, Amani Saleh Alrossies, Simon HL Hill, Adam J Potts, John RH Archer, Kerry Layne, Nicholas Webb, Luke de la Rue.

References

[1] Larson AM, Polson J, Fontana RJ, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology 2005;42(6):1364–72.
[2] Hospital Episode Statisitics. http://www.hscic.gov.uk/hes; 2011.
[3] Hawton K, Bergen H, Simkin S, et al. Long term effect of reduced pack sizes of paracetamol on poisoning deaths and liver transplant activity in England and Wales: interrupted time series analyses. BMJ 2013;346:f403.
[4] Ferner RE, Dear JW, Bateman DN. Management of paracetamol poisoning. BMJ 2011;342:d2218.
[5] Benefit risk profile of acetylcysteine in the management of paracetamol overdose. http://wwwmhragovuk/home/groups/pl-p/documents/drugsafetymessage/con184709pdf; 2012.
[6] Bateman DN, Dear JW, Thanacoody HK, et al. Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomised controlled trial. Lancet 2014;383(9918):697–704.
[7] Ferner RE, Langford NJ, Anton C, Hutchings A, Bateman DN, Routledge PA. Random and systematic medication errors in routine clinical practice: a multicentre study of infusions, using acetylcysteine as an example. Br J Clin Pharmacol 2001;52(5):573–7.
[8] Wong A, Sivilotti MLA, Gunja N, McNulty R, Graudins A. Accuracy of the paracetamol-aminotransferase product to predict hepatotoxicity in paracetamol overdose treated with a 2-bag acetylcysteine regimen. Clin Toxicol (Phila) 2018;56(3):182–8.
[9] Johnson MT, McCammon CA, Mullins ME, Halcomb SE. Evaluation of a simplified N-acetylcysteine dosing regimen for the treatment of acetaminophen toxicity. Ann Pharmacother 2011;45(6):713–20.
[10] Wong A, McNulty R, Taylor DM, et al. The NACSTOP trial: a multi-center, cluster-controlled trial of early cessation of acetylcysteine in acetaminophen overdose. Hepatology 2019;69(2):774–84.
[11] Thanacoody HK, Gray A, Dear JW, et al. Scottish and Newcastle antiemetic pretreatment for paracetamol poisoning study (SNAP). BMC Pharmacol Toxicol 2013;14:20.
[12] Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med 1998;17(8):873–90.
[13] Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. Pediatrics 1975;55:871–6.
[14] Wright N, Prescott LF. Letter: treatment of paracetamol poisoning. Br Med J 1975;2(5966):337.
[15] Cairney DG, Beckwith HK, Al-Hourani K, Eddleston M, Bateman DN, Dear JW. Plasma paracetamol concentration at hospital presentation has a dose-dependent relationship with liver injury despite prompt treatment with intravenous acetylcysteine. Clin Toxicol (Phila) 2016;54(5):405–10.
[16] Marks DJB, Dargan PI, Archer JRH, et al. Outcomes from massive paracetamol overdose: a retrospective observational study. Br J Clin Pharmacol 2017;83(6):1263–72.
[17] Dear JW, Clarke JI, Francis B, et al. Risk stratification after paracetamol overdose using mechanistic biomarkers: results from two prospective cohort studies. Lancet Gastroenterol Hepatol 2018;3(2):104–13.
[18] Whyte IM, Buckley NA, Reith DM, Goodhew I, Seldon M, Dawson AH. Acetaminophen causes an increased international normalized ratio by reducing functional factor VII. Ther Drug Monit 2000;22(6):742–8.

Please cite this article as: J.M. Pettie, T.M. Caparrotta, R.W. Hunter, et al., Safety and Efficacy of the SNAP 12-hour Acetylcysteine Regimen for the Treatment of Paracetamol Over..., , https://doi.org/10.1016/j.eclinm.2019.04.005